Clinical aspects of total intravenous anaesthesia: discussion paper[1]

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One may wish to use total intravenous anaesthesia to reduce the pollution hazard in the operating theatre, to avoid repeating the administration of potentially toxic drugs, or for specific indications where the inhalational technique is unsuitable. It may eventually become the method of choice where sophisticated modern equipment is not available, but as yet we have not progressed sufficiently with our understanding or our investigation of the technique to recommend it as a routine outside major centres. To most anaesthetists total intravenous anaesthesia means the administration of barbiturates or other induction agents throughout the period of anaesthesia, supplemented by a myoneural blocking drug and possibly with a potent narcotic and combining these with the continuous use of nitrous oxide/oxygen. Our knowledge of potent narcotics has increased dramatically in the last few years and, while we include high doses of analgesics under this heading, it is not always appreciated that nitrous oxide can be dispensed with while the patient is breathing oxygen-enriched air. This simplifies the method. For more than three decades anaesthetists have been using balanced anaesthesia, based on a drug which will induce sleep, one which will produce muscular paralysis and an analgesic or other means of suppressing reflex response to the operation. This has certainly achieved world-wide acceptance and there is no reason why the same principles should not apply to total intravenous anaesthesia.

Hypnotics: Over the years we have become aware of the occasional patient who, with conventional balanced anaesthesia based on an inhalational technique, has become aware of part of the operation (Wilson *et al.* 1975) although, with the use of large doses of potent narcotics, he may not have felt any pain during this period (Lowenstein 1971). This is undesirable and the danger of this occurring with total intravenous anaesthesia, where the conventional signs of lightening of anaesthesia may not be easily elicited, has made some anaesthetists apprehensive of adopting this technique. If one continuously gives a low concentration of halothane, methoxyflurane or enflurane throughout the procedure there is no danger of the patient remembering anything, but, as yet, a similar principle cannot readily be applied to intravenous agents. The use of premedicants or intravenous adjuvants which produce anterograde amnesia has also reduced the danger of recall during an operation but this seems, on first principles, to be a poor alternative to giving an adequate dose of anaesthetic. Lorazepam has a most potent amnesic action but may be rather longer-acting than one would wish (George & Dundee 1977); diazepam or midazolam have similar properties but only when given by the intravenous route (McKay & Dundee 1980).

Ketamine has the advantage of producing loss of consciousness with a profound analgesic action and there are still many occasions when this would be the drug of choice, but it does not produce muscular relaxation and recovery may be prolonged after the use of adequate doses. Dundee & Lilburn (1978) found that, when given for major surgery, the problems of psychotic sequelae following this drug are negligible and can be reduced by lorazepam premedication. Our experience with ketamine shows another aspect of these drugs: to get rapid control and reasonably rapid recovery, ideally those agents which induce sleep in one

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arm-brain circulation time should be used as the main hypnotic component of the anaesthetic. These could follow an initial dose of a benzodiazepine but then dosage would have to be reduced. This leaves the barbiturates (thiopentone and methohexitone) and etomidate. Both propanidid, which on theoretical grounds should have been an ideal drug for this purpose, and Althesin have recently been withdrawn from clinical use. Ledingham & Watt (1983) have expressed anxiety over the use of etomidate for prolonged procedures, thus leaving the two barbiturates. While thiopentone has been used for this purpose, its pharmacokinetic properties leave much to be desired, having an elimination half-life which is appreciably longer than that of methohexitone (Hudson *et al.* 1982), which would seem to be the barbiturate of choice. The use of Althesin has been widely recommended for this purpose (Savege 1979, Towler *et al.* 1982), although there may be a hazard from the effects of large doses of Cremophor: furthermore this drug could not safely be given to patients who have previously had a Cremophor-containing anaesthetic or who have a history of atopy or allergy (Clarke *et al.* 1975, Fisher & More 1981).

Relaxants: This second component of the balanced anaesthesia triad is so widely used by anaesthetists that it is only mentioned for the sake of completeness. There are a large number of well-tried and safe myoneural blocking drugs which can be given either by intermittent injection or by continuous infusion. The use of suxamethonium infusions has not gained much popularity in Britain although it is widely used in North America. When first embarking on total intravenous anaesthesia it is desirable not to change both the method of giving the hypnotic and the myoneural blocking drug for the technique can get very complicated with two or possibly three infusions running at the same time. Apart from the prolongation of the action of suxamethonium by propanidid (Clarke *et al.* 1964) and ketamine (Bovill *et al.* 1971), there are no other interactions between the induction agents and the myoneural blocking drugs.

Opioids: Anaesthetists are also experienced with the use of intermittent narcotic analgesics during anaesthesia and the newer drugs, fentanyl and alfentanil, would seem to have much to offer in this field. Alfentanil would seem to be a drug which is eminently suitable for use by an infusion (Hull 1983) but again one would not recommend anaesthetists to embark simultaneously on the use of two new techniques when first using total infusion anaesthesia.

The use of large doses of narcotics as sole agent or given with neuroleptic compounds such as droperidol, or with small doses of benzodiazepines, is too well established to require elaboration (*Lancet* 1979, Wood 1978). However, as previously mentioned, there are reports of patients who, despite the use of seemingly large doses of these drugs, do recall parts of the anaesthesia and, for this reason, their use should be preceded with a small dose of a benzodiazepine or a conventional induction agent; alternatively the 'depth' of anaesthesia should be monitored by an appropriate means (Maynard *et al.* 1969, Savege 1979).

Assuring unconsciousness

The 'missing link' in total intravenous anaesthesia is a means of guaranteeing that the patient remains unconscious with the use of conventional agents, and for this reason steps have to be taken to ensure an adequate plasma concentration of these drugs. With the continuous administration of an intravenous anaesthetic there is a delay before a steady-state plasma concentration is achieved, the time being related to the elimination half-life of the drug ($t_{\frac{1}{2}\beta}$): increasing the concentration or the rate of administration will only affect the plasma level and the time to achieve equilibrium cannot be shortened by this means (Greenblatt & Koch-Weser 1975). Two techniques have been recommended to overcome this: the simplest one is to give a standard induction dose of the intravenous agent followed by the infusion: here, plasma concentration may drop to unacceptably low levels following the induction dose, before the effect of the infusion becomes evident. A second method is to start with a rapid infusion which abruptly decreases to the rate required to maintain the

Table 1. Mean values of pharmacokinetic data for methohexitone

	V_1 ($l\ kg^{-1}$)	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})
Breimer 1976	0.29	0.0425	0.056	0.02
McMurray *et al.* 1984	0.23	0.0415	0.061	0.02

desired plasma concentration (Wagner 1974). This technique is only applicable to agents with high therapeutic ratios such as Althesin or etomidate.

Infusion technique

The ideal intravenous drug input required to rapidly produce and maintain constant plasma levels of a drug was described in 1968 by Kruger-Theimer, namely a single loading dose in combination with an infusion whose rate declines exponentially towards that required to maintain the desired plasma levels. Boyes *et al.* (1970) have shown that an exponentially decreasing infusion may be produced by the mixing of two solutions of different concentrations. McMurray *et al.* (1984) have described a simple method of administering a continuous infusion of methohexitone, using the above principles, that rapidly produces and maintains constant plasma levels commensurate with effective anaesthesia. It was necessary, initially, to determine the plasma methohexitone concentration at which patients would remain anaesthetized. Studies with an initial bolus dose and a continuous infusion showed this to be 10 $\mu g\ ml^{-1}$. In these studies the pharmacokinetic properties of the drug were also determined (Table 1), giving values which generally agreed with those of Breimer (1976). These two prerequisites of a target plasma concentration and reliable pharmacokinetic data are essential for any effective infusion technique.

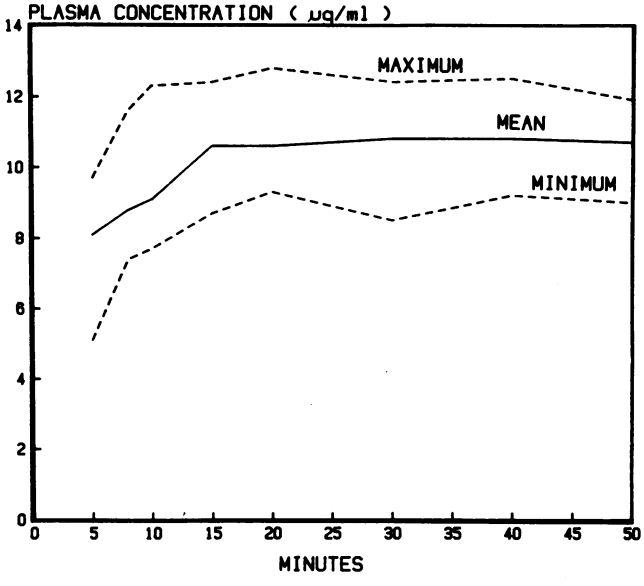

Figure 1. Plasma concentration-time profile obtained using a new method of administering a continuous infusion of methohexitone (McMurray *et al.* 1984). The solid line represents the mean plasma concentration ($n=9$); the upper and lower dashed lines represent the maximum and minimum plasma concentrations obtained at any one time

In principle, our technique involved the infusion of a dilute solution of methohexitone through a fine-bore needle, at a constant rate into a sealed glass mixing chamber (a multidose vial) containing a more concentrated solution of the drug. Infusion through the fine-bore needle created sufficient turbulence to ensure adequate mixing and the resultant exponentially decreasing mixture was displaced into the patient, producing a remarkably constant plasma concentration as shown in Figure 1. Even the lowest concentration ($8\ \mu g\ ml^{-1}$) achieved at 10 minutes was sufficient to ensure that the patient would not be awake.

The plasma levels in Figure 1 were achieved using a loading dose, infusion rate and concentrations of the two solutions which were calculated using the mean pharmacokinetic constants of Breimer (1976) and our own studies. This method has the further advantages of requiring no adjustment once the infusion is commenced and of using inexpensive materials readily available in any anaesthetic room.

This simple method of drug administration can be adapted to any situation but, like any other technique, one has to become familiar with it. As with all of these techniques, it should only be used by those who have an understanding of the underlying pharmacokinetics of the agents involved. Perhaps this may seem to put limitations on the use of the technique, but it should not be forgotten that whereas some 20 or 30 years ago anaesthetists were not aware of the pharmacokinetics of the inhalational agents, this is something which they have now learnt in great detail and which has been studied with each new drug. A similar understanding of intravenous agents is well within their capabilities.

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